DESIGN, DEVELOPMENT AND EVALUATION OF TRANSFEROSOME LOADED GEL DRUG DELIVERY SYSTEM

A

SYNOPSIS

SUBMITTED TO THE

SWAMI RAMANAND TEERTH MARATHWADA UNIVERSITY, NANDED

FOR THE DEGREE

OF

DOCTOR OF PHILOSOPHY

IN

PHARMACEUTICAL SCIENCES

UNDER

THE FACULTY OF SCIENCE & TECHNOLOGY

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2024

Synopsis submitted for Registration of Ph.D. in Pharmaceutical Sciences under

SWAMI RAMANAND TEERTH MARATHWADA UNIVERSITY, NANDED.

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DESIGN, DEVELOPMENT AND EVALUATION OF TRANSFEROSOME LOADED GEL DRUG DELIVERY SYSTEM

1. INTRODUCTION

1.1 Introduction to Transdermal Drug Delivery System:

Recent research is focused on the creation of novel drug delivery systems with patient compliance as the primary goal and high therapeutic activity. Drugs taken orally encounter a hostile environment in the GI tract, where the majority of medications are destroyed under acidic or alkaline conditions, have solubility problems, and, most significantly, undergo first-pass metabolism. Parenteral preparation has several drawbacks, including a lack of medication reversal, hypersensitive reaction, infection risk, and cost. Some medications are particularly bitter to the taste, making oral administration difficult for patients, and parenteral administration painful due to the necessity for a needle [1]. Because of the variety of benefits of this method, extensive research has been spent on the advancement of topical medication administration during the previous few decades. The skin on an average adult body covers roughly 2 m^2 and weighs 3 kg; it gets around one-third of the blood circulating throughout the body. Topical drug delivery refers to the application of a drug to the skin for a localized effect, whereas transdermal drug delivery systems (TDDS) employ the skin as a potential route for the administration of pharmaceuticals with systemic action. One of the systems with the highest patient compliance is TDDS. Some potential benefits of the transdermal route over other traditional routes include avoiding first-pass metabolism in the same way that oral and parenteral medications do, extending the duration of activity and minimizing unfavourable side effects, using medications with short half-lives, improving physiological and pharmacological response, preventing drug level fluctuations, inter and intra-patient variations, and most importantly, it offers patients convenience [2,3]. It also has certain disadvantages, such as the localized inflammation, erythema, itching, and restricted stratum corneum permeability. The stratum corneum's capacity to obstruct drug transport is a significant obstacle to dermal and transdermal delivery of drugs, rendering both approaches unsuitable for medical use [4]. The stratum corneum, or top layer of the epidermis, is composed of flattened, keratinized pieces of previously actively dividing epidermis. It is resistant and acts as a strong, flexible membrane. One of the most promising ways is to develop innovative vesicular carriers for drug administration through the skin, which allows the medicine to be delivered in a controlled manner [5-10]. Various technologies and systems, such as electrophoresis, iontophoresis,

chemical permeation enhancers, microemulsions, and sonophoresis, as well as using vesicular systems like liposome, niosomes, ethosomes, and transfersomes, have been investigated to evade this.

1.2 Transfersome:

In 1991, Gregor Cevc came up with the term "Transfersome" and the underpinning concept. A Transfersome is a complex agglomeration that is very adaptable and responsive to stress. An ultra-deformable vesicle with a highly complex lipid bilayer entrapping an aqueous core in its preferred form. Because the local composition and form of the bilayer are dependent on one another, the vesicle is self-regulating and self-optimizing. This enables the Transfersome to easily navigate a range of transportation challenges and function as a drug carrier for non-invasive targeted medicine administration and sustained release of therapeutic substances. The transfersome carriers are applied on the skin topically and are designed to attain high medication concentration at the point of delivery or nearby, increasing drug potency and reducing side effects [11]. Transfersomes were developed in order to utilize phospholipid vesicle as transdermal drug transporters. With their ultra-flexible membrane, these self-optimized aggregates can distribute medication into or through the skin in a reproducible manner, regardless of the method of administration or application. These vesicular transfersomes are more flexible than conventional liposomes, making them excellent for skin penetration.

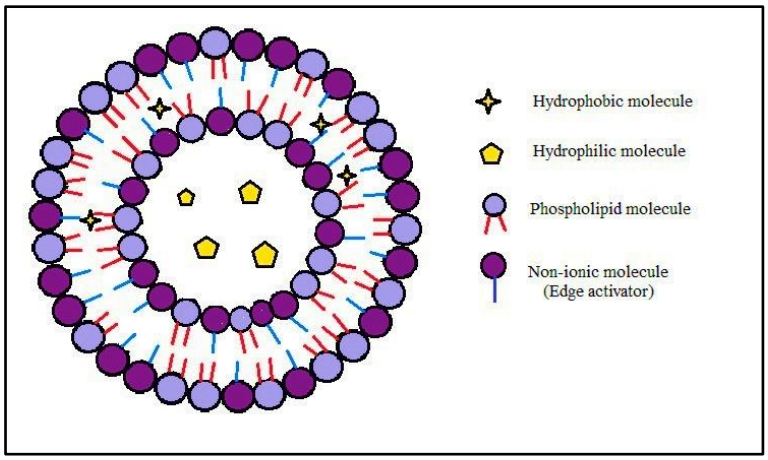

Figure no 1.1 Structure of transfersome

Transfersomes squeeze along the stratum corneum's intracellular barrier lipid to circumvent the skin's physical barriers to penetration. Due to the high degree of vesicle deformability, which permits entrance due to environmental physical stress in a self-adapting way. The membrane of transfersomes is made flexible by combining the proper surface-active substances

in the right amounts. As transfersomes may preserve the naturally occurring water gradient all across epidermis when employed under nonocclusive settings, there is less possibility of a full vesicles rupture in the skin. Transfersomes can enter the intact skin barrier by themselves through one of the two intra - cellular channels with unique bilayer characteristics. Two intracellular lipid routes with different bilayer properties can both spontaneously allow transfersomes to penetrate the intact stratum corneum [12].

To enhance the effectiveness of vesicle penetration across the skin, it is required to reduce the cost of each type of vesicle. It was accomplished by changing the lipid bilayer composition till the maximum tolerated vesicle surface flexibility was reached. Transfersomes are the result of such an optimization. Because of their hyper flexibility, the transfersomes can transfer up to 0.1 mg of lipid per hr and cm_2 through intact skin when applied under the right conditions. Furthermore, transfersomes can efficiently transport water-soluble molecules like proteins or polypeptides across the epidermis. This osmotic gradient, which is a result of the skin penetration barrier, inhibits water loss through evaporation and retains a water activity differential between the stratum corneum, which is close to the skin surface and has a virtually entirely dry stratum corneum (75% water content) [13, 14].

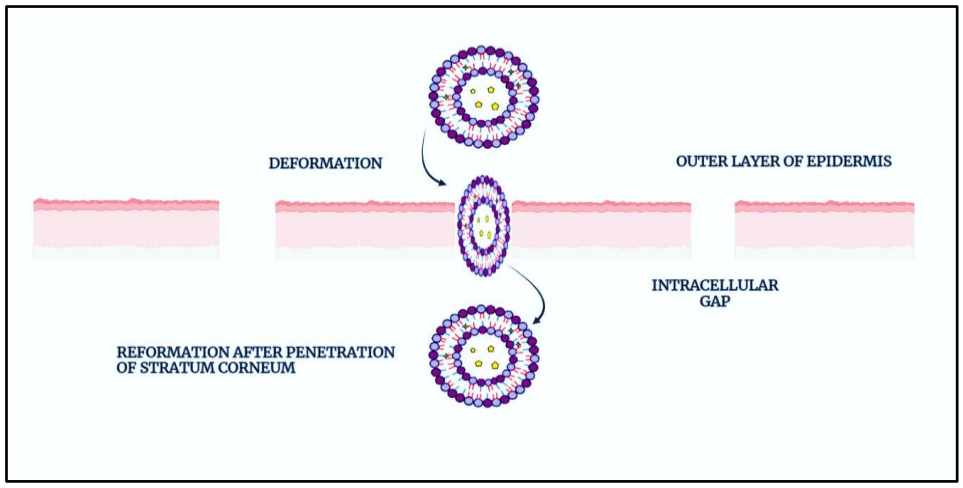

Figure no 1.2 Mechanism of transfersome penetration through skin

Even when the transdermal water loss is unphysiologically large, ambient air is a great sink for the water molecule, making this gradient exceedingly stable. Since the hydrophilic lipid residues and their nearby water interact favorably energetically, all polar lipids exhibit some water affinity. Thus, the majority of lipid bilayers resist induced dehydration on their own. As a result, every lipid vesicle produced from polar lipid vesicles moves from the relatively dry region to the sites with a significant amount of water concentration. The lipid vesicles sense

this "osmotic gradient" and attempt to move along it to avoid drying out completely when transfersomes are applied to the skin surface, which has already lost some moisture due to water evaporation. They can only do so if they are adequately flexible to pass through the skin's tiny pores because surfactant-based transfersomes have better rheologic and hydration qualities than those responsible for their increased deformability. Regular liposomes, which are less flexible vesicles, are restricted to the surface of skin, where they dry and fuse, making them less able to penetrate than transfersomes. Transfersomes are optimized in this regard, achieving maximal flexibility and so taking full use of the trans epidermal osmotic gradient [15].

Table no. 1.1 Different additives used in formulation of transfersomes

Ingredients	Example	Use
Phospholipids	Soya phosphatidylcholine, egg phosphatidylcholine	Vesicles forming component
Surfactant	Sod. cholate, Sod. deoxycholate, Tween-80, Span-80	Providing flexibility
Alcohol	Ethanol, methanol	Solvent
Buffering agent	Saline phosphate buffer (pH 7.4)	Hydrating medium

1.2.1 Methods of preparation:

1. Thin film hydration
2. Modified Handshaking Method
3. Vortexing sonication method
4. Reverse-phase evaporation method
5. Ethanol injection method
6. Freeze-thaw method

1.3 Introduction to Gel: [16,17]

Gels are semi-solid structures with liquid-interpenetrating large organic molecules or tiny inorganic molecules. Gel is a two-component, cross-linked three-dimensional network composed of structural materials interposed by an acceptable but proportionally enormous volume of liquid to build an endless rigid network structure that immobilizes the liquid continuous phase within. The structural ingredients that make up the gel network might be made up of inorganic particles or organic macromolecules, typically polymers. Cross connections can be established by chemical or physical interactions. This results in gel

classification into chemical and physical gel systems. Chemical gels are formed by permanent covalent bonding, whereas physical gels are formed by relatively weaker and reversible secondary intermolecular forces such as hydrogen bonding, electrostatic contacts, dipole-dipole interactions, Vander Waals forces, and hydrophobic interactions. Gels are defined by the USP as a semisolid system composed of a dispersion of either small inorganic particles or big organic molecules enclosed and interpenetrated by liquid. Gels are a two-phase system in which inorganic particles are not dissolved but rather scattered throughout the continuous phase and big organic particles are dissolved in the continuous phase and randomly coiled in the flexible chains.

1.3.1 Classification of Gel

- Based on nature of solvent:

a) Hydrogels: water is dispersion medium.
b) Organogels: organic solvent is dispersion medium.
c) Xerogels: highly porous solid formed from a gel by drying or removal of solvent.

- Based on physical nature:

a) Elastic gels: exhibit an elastic behavior.
b) Rigid gel.

1.3.2 Characteristics of gel

1. Swelling: When a gelling agent comes into contact with a liquid that solvates it, the agent absorbs a significant amount of the liquid and its volume increases. This is referred to as swelling. This effect is caused by solvent penetration into the matrix.
2. Syneresis: Many gels suddenly compress and release some fluid medium when left standing. This is referred to as syneresis. As the concentration of gelling agent diminishes, the degree to which syneresis occurs increases.
3. Ageing: Colloidal systems typically exhibit sluggish aggregation. This is referred to as ageing. Ageing causes a denser network of the gelling ingredient to grow gradually in gels.
4. Structure: The presence of a network created by the interlinking of gelling agent particles results in the stiffness of a gel. The particle's nature and the stress straighten them out and reduce the barrier to flow.

1.3.3 Method of preparation of gel

1. Fusion Method: A number of waxy compounds are used as gelling agents in non-polar fluids in this process. Drugs are introduced when waxy materials melt through fusion. Stir gradually until a smooth gel develops.
2. Cold Method: A mixing container is filled with cooled water (4 to 10 °C). The gelling ingredient is gradually incorporated via agitation. Maintain a temperature of less than 10 °C. The drug is progressively introduced in solution form while being gently blended.
3. Dispersion Method: The water is swirled while the gelling ingredient is spread. The non-aqueous solvent dissolves both the preservative and the medication. This solution is constantly agitated as it is poured into the gel above.

2. LITERATURE REVIEW

An extensive literature review on the proposed topic was conducted using the internet, review articles, research articles, journals, book chapters, and publications. According to the survey, no work has been done on the proposed topic, but some related work is listed below.

2.1 LITERATURE SURVEY ON SYSTEM

Abdallah et. al, (2022) aimed to develop transfersomal gel which could be an effective carrier for silymarin transdermal delivery. Silymarin was effectively added to transfersomal vesicles to increase drug skin permeability, which increased the drug's hypoglycemic efficacy [18].

Moqejwa et. al, (2022) goal of the current study was to evaluate the viability of using transfersomes to encapsulate cannabidiol for rectal drug administration. Successfully synthesized nano-sized cannabidiol-loaded Transfersomes were combined into a rectal colloid to improve the rectal absorption of cannabidiol in the therapy of aphagia [19].

2.2 LITERATURE SURVEY ON ADDITIVES:

Fitria et. al, (2022) observed that in drug permeability was an issue. Both bioavailability and penetration were highly enhanced by transfersomal emulgel compared to the non-transfersomal emulgel. This showed that the transfersomal emulgel is a promising vesicle for transdermal delivery [20].

Jamadar et. al, (2022) aimed to improve the permeability of the drug by encapsulating it in transfersome. The skin permeation and deposition studies indicated that the gel improved permeability in the skin compared to the Hydroquinone plain gel [21].

2.3 LITERATURE SURVEY ON METHODS:

Luiz et. al, (2021) used the thin-film hydration method for transfersomes development that had a narrow particle size distribution and high encapsulation efficiency in glioblastoma multiforme treatment (Brain Tumor) [22].

Wu et. al, (2019) used high-pressure homogenization technique that improves the transfersome bioavailability with optimal particle size 40.13 ± 0.51 nm of resveratrol transfersomes formulation prepared for antioxidant activity [23].

3. DRUGS PROFILE[24]

3.1 Ebastine

Ebastine is a second-generation H1-receptor antagonist with an oxypiperidine-based structure, and its active form is the metabolite carebastine.

Drug Name: Ebastine

Functional category: Anti- histamine

Molecular Formula and weight: $C_{32}H_{39}NO_2$ and 469.658 g/mol

Chemical IUPAC Name: 4-(4-benzhydryloxy-1-piperidyl)-1-(4-tert-butylphenyl) butan-1-one

Structure:

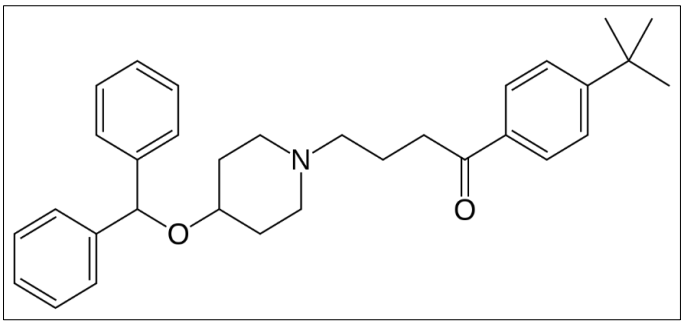

Figure no 3.1 Structure of Ebastine

Appearance: White crystalline powder

Description: Ebastine is an effective anti-allergic medicine used to relieve the symptoms caused by allergic reactions such as urticaria or allergic rhinitis. The symptoms may include sneezing, runny nose, itchy eyes, skin rashes, redness of the eyes, etc

Mechanism of action: Ebastine is a second-generation piperidine H1-antihistamine. H1-antihistamines interfere with the agonist action of histamine at the H1 receptor and are administered to attenuate inflammatory process in order to treat conditions such as urticaria, allergic rhinitis, allergic conjunctivitis, and urticaria. Reducing the activity of the NF-κB immune response transcription factor through the phospholipase C and the phosphatidylinositol (PIP2) signaling pathways also decreases antigen presentation and the expression of pro-inflammatory cytokines, cell adhesion molecules, and chemotactic factors. Furthermore, lowering calcium ion concentration leads to increased mast cell stability which reduces further histamine release. Second-generation antihistamines are more selective for H1-receptors of the

peripheral nervous system (PNS) and do not cross the blood-brain barrier. Consequently, these newer drugs elicit fewer adverse drug reactions.

3.2 Montelukast sodium

Drug Name: Montelukast sodium

Functional category : antiasthmatic (leukotriene receptor antagonist)

Molecular Formula and weight : C35H36CINO3S and 608.18 g/mol

IUPAC NAME: 2-[1-({[(1R)-1-{3-[(E)-2-(7-chloroquinolin-2-yl)ethenyl]phenyl}-3-[2-(2-hydroxypropan-2-yl)phenyl]propyl]sulfanyl}methyl)cyclopropyl]acetic acid.

Structure :

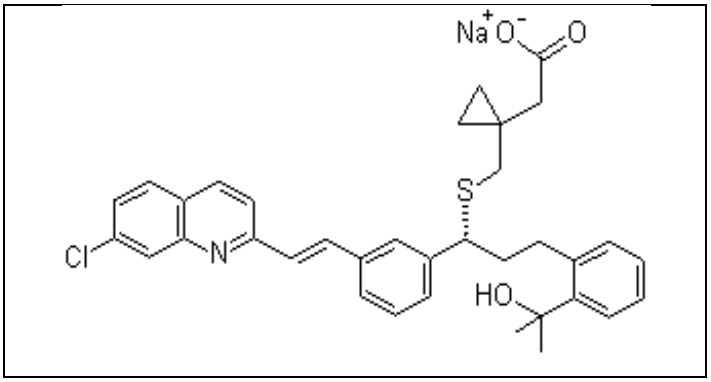

Figure no. 3.2: Structure of Montelukast sodium

Appearance: It is pale yellow powder with characteristic order.

Description: Montelukast was first approved for clinical use by the US FDA in 1998 as Merck's brand name Singulair. The medication is a member of the leukotriene receptor antagonist (LTRA) category of drugs.

Mechanism of action : Cysteinyl leukotrienes (CysLT) like LTC4, LTD4, and LTE4, among others, are eicosanoids released by a variety of cells like mast cells and eosinophils. When such CysLT bind to corresponding CysLT receptors like CysLT type-1 receptors located on respiratory airway smooth muscle cells, airway macrophages, and on various pro-inflammatory cells like eosinophils and some specific myeloid stem cells activities that facilitate the pathophysiology of asthma and allergic rhinitis are stimulated. Subsequently, Montelukast is a leukotriene receptor antagonist that binds with high affinity and selectivity to the CysLT type

1 receptor, which consequently assists in inhibiting any physiological Action of CysL Ts LTC4, LTD4, and LTE4 at the receptor that may facilitate asthma or allergic rhinitis.

4. AIM AND OBJECTIVE OF RESEARCH WORK

4.1 Aim

The aim of the present study is to formulate and evaluate drug-loaded transfersomal gel using the QbD approach.

4.2 Objectives

The research work is planned by taking into consideration the following specified objectives.

- To perform identification and confirmation of drug.
- To perform preformulation study.
- To optimize formulation and process variables using QbD approach (Box-Behnken model)
- To develop and formulate the drug-loaded transfersomes by using thin film hydration method.
- To evaluate and the drug-loaded transfersomes.
- To formulate transfersomal gel by using suitable gelling agent.
- To evaluate of transfersomal gel formulation.
- To study In-vitro drug diffusion using a suitable membrane model using a simple diffusion cell, Kinetic study etc.
- To perform stability studies.

4.3 Rationale behind selection of drugs

Ebastine is a second-generation H1-receptor antagonist and BCS II (low solubility and high permeability) effective anti-allergic medicine used to relieve the symptoms caused by allergic reactions such as urticaria and its oral bioavailability is 40%. The purpose of selecting drug is to improve its bioavailability by incorporating drug in transfersomal gel formulation.

Montelukast sodium is an anti-asthmatic (leukotriene receptor antagonist). Montelukast sodium is an orally available leukotriene receptor antagonist which is widely used for the prophylaxis and chronic treatment of asthma and has been linked to rare cases of clinically apparent liver injury. Not use for treatment of bronchospasm in acute asthma attacks. Montelukast is usually administered orally. Montelukast blocks the action of leukotriene D4 on the cysteinyl leukotriene receptor CYSLT1 within the lungs and bronchial tubes by binding to it. The reduces the bronchoconstriction otherwise caused by the leukotriene and results in

less inflammation. These problems can be improved by reformulating the drug delivery via a different route like skin. However, conventional topical dosage forms, mostly of which are present in the gel form, usually have quite limited therapeutic efficacy due to the low bioavailability as a small fraction of drug cross the skin barrier. Nowadays, niosomes play an increasingly important role by acting as a carrier for delivery of drug across skin. Niosomes are dispersed uniformly into gel base (hydrogel) to form niosomal gel. It has gained considerable attention in recent years as one of the most promising vesicular drug delivery systems owing to their unique potential via combining the characteristics of a hydrogel system with niosomes. Several polymeric hydrogel niosomes systems have been prepared and characterized in recent years, but among them carbopol 934 is been studied extremely for preparing of niosomal gel. Niosomes have ability to reduce side effect, modify drug pharmacokinetics, increase bioavailability, increase residence time of drug along with the site-specific drug delivery specially in case of trichomoniasis, bacterial vaginosis, non –gonococcal urethritis whose symptoms are seen superficially on external body surface. Niosomal gel seems an interesting drug delivery system in the treatment of parasitic infection especially protozoal infections. Niosomes are the non –ionic surfactant based vesicular system which may enhance bioavailability, and encapsulation of the drug in the niosome can improve the permeation. Niosome gel are used to achieve optimal cutaneous and percutaneous drug delivery. They can avoid a gastrointestinal drug absorption difficulty which is due to gastrointestinal pH. Gels are having property to avoid enzymatic activity and drug interaction with food and drinks.

5. PLAN OF WORK

5.1 Literature Survey

5.2 Identification and Confirmation of Drug and Excipients

a) Organoleptic properties (Colour, Odour, Appearance)

b) Melting point

c) Ultraviolet Visible Spectrophotometry

d) Fourier Transform Infra-Red (FTIR) Spectroscopy

5.3 Preformulation Studies

5.4 Design and Optimization

5.5 Formulation and Optimization of Transfersomes

5.6 Evaluation of Transfersomes

5.7 Preparation of Transfersomal Gel

5.8 Evaluation of Transfersomal Gel

5.9 Drug Release Kinetics

5.10 Stability Studies

5.11 Compilation of Data

6. Possible outcomes

Successful design of a transferosome-loaded gel that ensures stability, efficient drug encapsulation, and controlled release.

7.Duration of study

Sr.No.	Duration(in month)	Activity
1	0-6	Literature survey
2	6-12	Procurement of API and excipients
3	12-16	Preformulation study,optimization of transferosomes
4	18-24	Preparation and evaluation of transferosomal gel
5	24-30	Drug release kinetics and stability study
6	30-36	Compilation of data and submission of thesis

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